BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,872	04/25/2001	Antonio J. Grillo-Lopez	P 0280609/2000-30-154A	4921

909 7590 12/12/2003

PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 12/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,872	GRILLO-LOPEZ, ANTONIO J.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7 and 51-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7 and 51-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Request for Continued Examination

The request filed on September 26, 2003 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/480872 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 2, and 6, and 8-50 were cancelled.

Claims 51-60 were added.

Claims 1, 3-5, 7, and 51-60 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claims 1, 7, 51 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Maloney *et al.* (Blood, Vol. 90. No. 6, 1997, pages 2188-2195.) for the reasons of record. With regards to Claims 1 and 7, Applicants arguments (Paper No. 13, pages 5-6) are substantially the same as those presented after-final (Paper No. 10) and remain rejected for the reasons of record in Paper No. 11, page 2. New claims 51 and 55 include "whereby growth of a CNS lymphoma is reduced" (Claim 51) which is anticipated by Maloney *et al.* since the growth of the lymphoma cells was reduced by administering to the patients a therapeutically effective amount of an anti-CD20 antibody.

Claims 1, 5, 7, 51, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maloney *et al.* (Blood, Vol. 90. No. 6, 1997, pages 2188-2195.) as further evidenced by Yoneda *et al.* (US Patent No. 5,626,845, 1997). Applicant's arguments (Paper No. 13, page 6, last paragraph) are substantially the same as those presented after-final (Paper No. 10) and remain rejected for the reasons of record in Paper No. 11, page 2 and for the reasons of record set forth above.

New Rejections

Claims 1, 3-5, 7, and 51-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,776,456 (Anderson *et al.*) in view of U.S. Patent No. 6,042,826 (Caligiuri *et al.*) and DeAngelis, LM (J.Neurooncol. Vol. 38'(2-3), 1998, pages 245-252).

US Patent No. 5,776,456 teaches methods of treating B cell lymphomas comprising administering a therapeutically effective amount of a chimeric anti-CD20 antibody to a humans (column 5).

The patent does not specifically teach treating a central nervous system lymphoma wherein the CNS lymphoma is selected from the group consisting of: primary CNS lymphoma, leptomeningeal metastasis (LM), or Hodgkin's Disease with CNS involvement; wherein the anti-CD20 antibody fragment is selected from the group consisting of Fab, Fab', and $F(ab')_2$. The patent further fails to specifically teach treating LM with the anti-CD20 antibody in combination with cytarabine and thiotepa or methotrexate and ^{111}In-diethylenetriamine pentaacetic acid.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the methods of Anderson *et al.* (US Patent No. 5,776,456) so as to include the treatment of B-cell lymphomas located in the central nervous system (CNS) because CNS lymphomas represent a species of the genus B-cell lymphomas successfully treated by Anderson *et al.* One of ordinary skill in the art need only be motivated to treat such CNS lymphomas by a demonstration in the relevant art that such lymphomas can be successfully treated in a manner similar to the claimed invention. Here, Caligiuri *et al.* (US Patent NO. 6,042,826) teach a method for treating a primary central nervous system B-cell lymphoma by administering a chimeric monoclonal antibody. Although the targeted antigens are different (CD20 versus Fas), the references, taken together, would suggest to one of ordinary skill a reasonable expectation of success that CNS lymphomas would also be successfully treated by administration of the antibodies utilized by Anderson *et al.* Further, it would have been obvious to one of skill in the art to substitute the antibody of Anderson *et al.* with antibody fragments such as Fab, Fab' and F(ab')2 because Anderson *et al.* teaches that methods for producing such various fragments are well known to those skilled in the art (column 3, line 30).

Further, the teachings of Caligiuri *et al.* recognize that primary central nervous system lymphomas involve the meninges (column 2, line 10) wherein it is well known in the art that lymphomas are common causes of leptomeningeal metastasis (DeAngelis, left column, page 245). Hence, one of ordinary skill in the art would have a reasonable expectation that a subpopulation of patients with a CNS lymphoma would also exhibit leptomeningeal metastasis. Combining chemotherapy with other known anti-neoplastic agents is well known in the art. Caligiuri *et al.* recommends combinatorial chemotherapy with the administered antibodies

(column 13, lines 1-12). The teachings of DeAngelis are specific to LM wherein only three chemotherapeutic agents are widely used- methotrexate, cytarabine, and thiotepa which are usually administered in conjunction with an agent which measures CSF flow impairment in the CSF- ^{111}In-diethylenetriamine pentaacetic acid (DTPA)—see column 2, page 249. Hence, it would be obvious to one of ordinary skill in the art to administer the anti-CD20 antibody of Anderson *et al.* in combination with the above chemotherapeutics for treating a CNS lymphoma that exhibits leptomeningeal metastasis. Further, although the prior art does not specifically characterize that levels of the anti-CD20 antibody are greater in CSF than in serum (Claim 56), such an observation would be obvious to one of ordinary skill because the administered antibodies are distributed in the CSF.

Claims 1, 3-5, 7, and 51-60 are also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,776,456 (Anderson *et al.*) in view of the teachings of U.S. Patent No. 6,042,826 (Caligiuri *et al.*) and DeAngelis, LM (J.Neurooncol. Vol. 38 (2-3), 1998, pages 245-252).

Claim 1 of US Patent No. 5,776,456 is drawn to a method of treating a B cell lymphoma comprising administering a therapeutically effective amount of immunologically active chimeric anti-CD20 antibody to a human, said antibody being derived from a transfectoma comprising anti-CD20 in TACE 9, ATCC deposit number 69119.

The above claim constitutes a genus of B-cell lymphomas and a species of anti-CD20 antibody (TACE 9, ATCC deposit number 69119). Since the currently pending claims constitute a genus of anti-CD20 antibodies, the patented species of anti-CD20 antibody (TACE 9, ATCC

deposit number 69119) is an obvious variation included in the genus pending claim. Further, the patented claims represent a genus of B-cell lymphomas while the pending claims are drawn to treating species of B-cell lymphomas, i.e. those involving the central nervous system. Thus, the species of PCNSLs, leptomeningeal metastasis, or Hodgkin's disease with CNS involvement, anticipates the broader genus of the patented claims drawn to a method of treating *all* B-cell lymphomas.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the methods of Anderson *et al.* (US Patent No. 5,776,456) so as to include the treatment of B-cell lymphomas located in the central nervous system (CNS) because CNS lymphomas represent a species of the genus B-cell lymphomas successfully treated by Anderson *et al.* One of ordinary skill in the art need only be motivated to treat such CNS lymphomas by a demonstration in the relevant art that such lymphomas can be successfully treated in a manner similar to the claimed invention. Here, Caligiuri *et al.* (US Patent NO. 6,042,826) teach a method for treating a primary central nervous system B-cell lymphoma by administering a chimeric monoclonal antibody. Although the targeted antigens are different (CD20 versus Fas), the references, taken together, would suggest to one of ordinary skill a reasonable expectation of success that CNS lymphomas would also be successfully treated by administration of the antibodies utilized by Anderson *et al.* Further, it would have been obvious to one of skill in the art to substitute the antibody of Anderson *et al.* with antibody fragments such as Fab, Fab' and F(ab')2 because Anderson *et al.* teaches that methods for producing such various fragments are well known to those skilled in the art (column 3, line 30).

Further, the teachings of Caligiuri *et al.* recognize that primary central nervous system lymphomas involve the meninges (column 2, line 10) wherein it is well known in the art that lymphomas are common causes of leptomeningeal metastasis (DeAngelis, left column, page 245). Hence, one of ordinary skill in the art would have a reasonable expectation that a subpopulation of patients with a CNS lymphoma would also exhibit leptomeningeal metastasis. Combining chemotherapy with other known anti-neoplastic agents is well known in the art. Caligiuri *et al.* recommends combinatorial chemotherapy with the administered antibodies (column 13, lines 1-12). The teachings of DeAngelis are specific to LM wherein only three chemotherapeutic agents are widely used- methotrexate, cytarabine, and thiotepa which are usually administered in conjunction with an agent which measures CSF flow impairment in the CSF- ^{111}In-diethylenetriamine pentaacetic acid (DTPA)—see column 2, page 249. Hence, it would be obvious to one of ordinary skill in the art to administer the anti-CD20 antibody of Anderson *et al.* in combination with the above chemotherapeutics for treating a CNS lymphoma that exhibits leptomeningeal metastasis. Further, although the prior art does not specifically characterize that levels of the anti-CD20 antibody are greater in CSF than in serum (Claim 56), such an observation would be obvious to one of ordinary skill because the administered antibodies are distributed in the CSF.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
December 10, 2003